ZOOLOGICAL RESEARCH

Stem cell therapy for Parkinson's disease using non-human primate models

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ABSTRACT

Stem cell therapy (SCT) for Parkinson's disease (PD) has received considerable attention in recent years. Non-human primate (NHP) models of PD have played an instrumental role in the safety and efficacy of emerging PD therapies and facilitated the translation of initiatives for human patients. NHP models of PD include primates with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) -induced parkinsonism, who are responsive to dopamine replacement therapies, similar to human PD patients. Extensive research in SCT has been conducted to better treat the progressive dopaminergic neurodegeneration that underlies PD. For effective application of SCT in PD, however, a number of basic parameters still need to be tested and optimized in NHP models, including preparation and storage of cells for engraftment, methods of transplantation, choice of target sites, and timelines for recovery. In this review, we discuss the current status of NHP models of PD in stem cell research. We also analyze the advances and remaining challenges for successful clinical translation of SCT for this persistent disease.

Keywords: Stem cell therapy; Non-human primates; Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder that results from progressive loss of dopaminergic (DA) neurons in the substantia nigra of the midbrain. This loss is associated with characteristic motor dysfunction, including bradykinesia, rigidity, and rest tremor. The molecular hallmark of PD is the presence of Lewy bodies (LBs) composed of the alpha-synuclein (α-syn) protein in the substantia nigra and cortical regions of the brain (Dauer & Przedborski, 2003). Treatment with the dopamine precursor levodopa can improve symptoms, but does not prevent DA neuron destruction (Kim et al., 2002). Although no cure is currently available, cell-based therapy (CBT) (in which cellular material, usually intact, living cells such as T cells capable of fighting cancer via cell-mediated immunity, is injected into the patient during immunotherapy) is considered one of the most promising methods for eradicating PD (Sonntag et al., 2018). Currently, stem cells are among the best cell sources for CBT.

Pioneering studies on the application of CBT in rodent models provided invaluable information on neuronal survival, migration, and post-grafting integration (Kim et al., 2013). Nevertheless, clinical translation of CBT for PD requires further investigation and evaluation in different species. Experiments in NHP models are ideally suited for such exceptional and invasive brain therapy (Didier et al., 2016).

Stem cells have the capacity to proliferate and differentiate into multiple cellular lineages, offering an enormous pool of resources for therapeutic applications such as autologous stem cell transplants (Drouin-Ouellet, 2014). Using stem cells to treat neurodegenerative diseases has become an area of intense interest. Current clinical applications of stem cells

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have targeted Alzheimer's disease (Kwak et al., 2018), PD (Parmar, 2018), amyotrophic lateral sclerosis (Robinson, 2018), and multiple sclerosis (Shirani & Stuve, 2018), and are predicted to increase in coming years. Furthermore, SCT has been proposed to counteract the characteristic massive loss in DA neurons observed in PD (Chiu & Hall, 2006).

Since the first clinical trials in the late 1980s using fetal midbrain tissue to replace lost DA neurons, hundreds of patients worldwide have been subjected to neural fetal tissue grafting, with many showing long-term graft survival, good clinical outcomes, and physiological release of dopamine over decades (Barker et al., 2017). Furthermore, the derivation of human embryonic stem cells (hESCs) (Thomson et al., 1998) provided a new scalable cell source for stem cell therapy (SCT), which may potentially replace fetal tissue. However, the road to clinical application of these cells has proven to be long, involving a number of key steps such as gaining control over cell subtype differentiation, producing safe and efficacious cells, adhering to good manufacturing regulations, scaling-up production processes, and obtaining regulatory approval of the final cell products.

Although CBT is the most promising treatment for a variety of neurodegenerative diseases, animal experiments remain limited. NHPs exhibit great similarity to humans in regard to genetics, brain/cognitive function and development, organs, metabolism, and drug susceptibility (Zhang et al., 2014). Therefore, experimental results from NHP-based studies are critical and convincing.

Since the early 1980s, scientists have relied on NHP models to assess the potential benefits of CBT for PD (Cowen, 1986). Compared to rodents, PD-relevant behavioral outcomes, such as fine motor skills, can be easily tested in NHPs (Camus et al., 2015). Clinically relevant behavioral parameters are critical for evaluating the efficacy of therapeutic strategies, such as the choice of intracerebral grafting targets (Bentlage et al., 1999; Kauhausen et al., 2015; Thompson et al., 2010). NHPs and humans show similar organization of the neo-striatum, with the caudate nucleus and putamen clearly delineated by white matter tracts of the internal capsule (Howson et al., 2019). In contrast, in rodents, the transecting white matter tracts of the internal capsule are broken into bundles (pencils of Willis) that perforate the entire striatum without presenting a distinct physical barrier for cell distribution (Coizet et al., 2017). Thus, NHP models have facilitated CBT progress toward clinical application.

Humans and NHPs possess similar behavioral elements, physiology, anatomy, biochemistry, organ mechanisms, and immune functions (Vierboom et al., 2012). Therefore, NHP models enable the translation of therapy-focused research from small animals to humans. In particular, NHP models of human disease provide exceptional opportunities to advance SCT by addressing pertinent translational concerns associated with this research, including the application of autologous/allogeneic-induced pluripotent stem cell (iPSC)-derived cellular products, immune responsivity, clinical delivery techniques, and evaluation of candidate cell line profiles following transplantation (Wang et al., 2017; Wei et al., 2016). Furthermore, NHP models offer unique possibilities to evaluate the complexity of the biochemical, physiological, behavioral, and imaging end points relevant to current human conditions (Koprich et al., 2017).

Given the ethical concerns, expense of specialized equipment, and necessity of highly trained staff, the value of using NHPs must be carefully assessed. Well-designed and less resource-demanding studies in small animal models, such as rodents, are essential for ultimately translating NHP model research into human patient therapy. Each disease-specific research community should focus on developing relevant NHP models that advance the translation of stem cell research and therapy.

In this review, we discuss the role of NHP models in developing SCT for PD, stem cell types that can be used for transplantation, and value of NHP studies in translating these therapies for clinical application.

NHP MODELS OF PD FOR SCT RESEARCH

Neurotoxin-induced models

The most commonly used neurotoxins for generating models of PD are 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

6-OHDA models

As a neurotoxic compound, 6-OHDA induces cell death via oxidative stress after uptake by the catecholamine transport system (Zhou & Cheng, 2019). 6-OHDA is commonly used in rodents as they are much less sensitive to MPTP compared with humans and NHPs. Although many researchers have reported that 6-OHDA can cause cell death *in vivo* (Bernstein et al., 2011; Tobón-Velasco et al., 2013), several studies have found no markers of cell death upon treatment with this compound (Kostrzewa, 2000), suggesting possible phenotype loss. In the application of 6-OHDA for PD model development, the severity of the resulting disease depends on the number, size, and location (e. g., striatum, substantia nigra, or medial forebrain bundle) of 6-OHDA injections (Emborg, 2004). Eslamboli et al. (2003) applied nine striatal injections of 6-OHDA to model PD in common marmoset monkeys; however, due to the spontaneous recovery of symptoms 10 weeks after surgery, Eslamboli et al. (2005) developed a new model using 18 unilateral intrastriatal injections.

One drawback of the above model is the numerous intracerebral needle passages necessary for appropriate 6-OHDA distribution to decrease the extent of spontaneous recovery (Santana et al., 2015). As with other stereotaxic procedures, this model requires surgical settings and trained personnel to perform brain surgery and provide recovery care.

MPTP models

Administration of MPTP is a classic method for generating PD due to the selective toxicity of this chemical toward DA neurons (Jiang & Dickson, 2018; Lei et al., 2016; Li et al., 2015a; Su et al., 2015). It is historically important in animal models of PD and provides utility to test certain CBT

parameters. After crossing the blood-brain barrier, MPTP is transformed by monoamine oxidase B into its active metabolite, 1-methyl-4-phenylpyridinium ion (MPP+), which is then carried by dopamine transporters into DA neurons of the substantia nigra pars compacta (SNpc), where the compound blocks mitochondrial complex I activity (Huang et al., 2018). Although it has limitations, MPTP treatment is the current standard in NHPs. The discovery of this mechanism of action in the 1990s paved the way for subsequent studies exploring mitochondrial function in PD and provided a prominent animal model of the disease (Emborg, 2017).

Pesticide/herbicide-induced modelsParaquat models

Paraquat is an important member of the bipyridylium family of broad-spectrum herbicides and is commonly used to control pests in important crops such as soybeans, sorghum, sugar cane, cotton, and corn. It interferes with photosynthetic electron transport and reduces oxygen to superoxide free radicals, leading to membrane rupture and leaf desiccation (Sarwar et al., 2015). Many countries have already banned paraquat due to its acute pulmonary and cutaneous toxicity or established restricted-use measures, such as limited concentrations of the active ingredient in formulated products and manipulation by licensed mixers and ground applicators only (Kuo & Yu, 1991). In experimental models, paraquat has been linked to the production of reactive oxygen species (ROS), oxidative stress, and aggregation of α-syn proteins in DA neurons (Kuter et al., 2007, 2010). However, the mechanism used by paraquat to access DA neurons is not yet fully understood (Vaccari et al., 2017; Zhou et al., 2017).

Rotenone models

As a mitochondrial toxin, rotenone can produce dose-dependent systemic toxicity and mortality (Sanders & Greenamyre, 2013). Following delivery of this compound (via osmotic minipump), a proportion of animals becomes parkinsonian, with different degrees of nigrostriatal lesions (Perier et al., 2003). Furthermore, rotenone (2–3 mg/kg/day) is reported to elicit selective nigrostriatal degeneration, generally without nonspecific lesions (Trigo et al., 2018). For example, Cicchetti et al. (2010) found that rotenone caused severe digestive issues, with an enlarged stomach full of undigested food, following systemic application. Although it was not recognized as such, this may have been the first indication that rotenone can reproduce the lesser-known gastrointestinal symptoms of PD, such as gastroparesis (Johnson et al., 2018). Indeed, Bové & Perier (2012) reported that rotenone accurately recapitulates the pathological and functional features of parkinsonian gastrointestinal impairment.

Although the reasons for the discrepancies between research results are uncertain, recent refinements of the rotenone model have made it more reproducible and reduced the number of nonspecific toxicities. Smirnova et al. (2016) demonstrated that withdrawal of rotenone led to counter-regulation of mir-7 and the *ASS1*, *CTH*, and *SHTM2* genes, suggesting a possible role of these genes in direct cellular responses to this toxicant and the suitability of the model at addressing the processes of resilience and recovery in neurotoxicology and PD. Furthermore, Cimdins et al. (2019) used rotenone, as a potent complex I-specific mitochondrial inhibitor, to determine the neuroprotective effects of APP and sAPPα *in vitro*, in neuronal cell lines over-expressing APP, and in a retinal neuronal rotenone toxicity mouse model *in vivo*. Overall, it is difficult to effectively model all aspects of a complex, age-related human disease such as PD in rats. Even genetically accurate models of PD have met limited success in replicating key behavioral and pathological features of the disease. Nevertheless, a great deal has been learned–and remains to be discovered–about the pathogenic mechanisms of PD using rotenone models of the disease.

Genetically engineered models

Genetic NHP PD models have been generated previously by intracerebral injection of viral vectors encoding mutant α-syn or administration of LB extracts (Marmion & Kordower, 2018). Nigral overexpression of human wild type or mutant A53T α-syn, induced by adeno-associated viral (AAV) vectors, has been shown to induce PD-like motor symptoms, significant nigral DA cell loss, and α-syn aggregates in common marmoset monkeys (Eslamboli et al., 2007; Kirik et al., 2003). AAV and lentiviral vectors encoding A53T α-syn have also been used in cynomolgus (Koprich et al., 2016) and rhesus monkeys (Yang et al., 2015). In both studies, expression of A53T α-syn led to nigral cell loss and α-syn accumulation and aggregation, though without behavioral changes. Furthermore, while AAV-induced overexpression of A53T α-syn and parkin, another PD-implicated protein, in cynomolgus monkeys led to a decrease in striatal DA markers and α-syn accumulation and phosphorylation, no PD motor symptoms were observed (Recasens et al., 2014). Notably, nigral injection of AAV expressing short hairpin RNA (shRNA) to knock down α-syn in vervet monkeys induced a region-specific decrease in tyrosine hydroxylase (TH)-positive nigral cell number and striatal innervation compared to animals that received scrambled shRNA, although no behavioral changes were reported (Collier et al., 2016). Intracerebral inoculation with α-syn fibrils has been extensively used in rodents, but not yet in monkeys (Luk et al., 2012; Paumier et al., 2015). On the other hand, cadaveric Lewy body extracts have been injected into the striatum and nigra of cynomolgus monkeys with and without previous treatment with MPTP (Recasens et al., 2014), which induced a variable decrease in striatal and nigral DA markers and an increase in α-syn expression, but no PD motor symptoms. It should be noted that, with the exception of AAV-mediated α-syn studies in marmosets, all investigations on genetically produced models have been performed using only a few subjects. Therefore, further characterization and validation of such models is necessary before they can be used as robust testing platforms for SCT.

Transgenic NHP models induced by injection of NHP oocytes with lentiviral vectors encoding PD-relevant proteins with mutations of interest have emerged in recent years. For example, transgenic rhesus monkeys overexpressing mutant A53T α-syn have been reported (Niu et al., 2015), with some

behavioral deficits observed at 1.5−2.5 years of age. New technologies such as CRISPR/Cas9-genomic editing also present an opportunity to generate NHP models with PD-associated mutations expressed at physiological levels, which may help clarify the mechanism of disease onset, including the development of motor and non-motor symptoms (Handschel et al., 2011; Luol et al., 2016). These novel NHP models may provide clues to better understand α-syn-related disorders and enable the development of SCT to treat them.

STEM CELLS AS SOURCES FOR CBT

Embryonic stem cells

Embryonic stem cells (ESCs) have attracted considerable attention as an alternative source for the generation of DA neurons. Handschel et al. (2011) described a technique for culturing ESCs in the absence of artificial scaffolds, which generated mineralized micromasses. This technique made it possible for ESCs to proliferate, which is a prerequisite for CBT. Due to their pluripotency and highly proliferative properties, ESCs can give rise to any type of cell in the body, including DA neurons (Thomson et al., 1998), which can be produced in sufficient numbers for transplantation therapy. ESCs are associated with the risk of tumorigenesis due to genomic instability in culture (Zhao et al., 2015), even if the cells appear to fully differentiate into DA neurons *in vitro* before transplantation (Luk et al., 2012). Myocyte enhancer factor 2 (MEF2C) directs the differentiation of mouse ESC-derived neural precursors into neurons (Skerjanc & Wilton, 2000). Furthermore, MEF2C confines hESCs to the neuronal lineage, which can be used to generate neurons and avoid tumor formation for use in SCT (Eslamboli et al., 2005). Human and rodent ESC-derived DA neurons have been shown to survive transplantation into the striatum of parkinsonian NHPs and generate a degree of functional recovery (Hayashi et al., 2013).

Nevertheless, studies have shown that the survival of ESC-derived DA neurons post transplantation is relatively low. Li et al. (2017) demonstrated that hESCs differentiated into DA neurons when co-cultured with PA6 cells, with almost 92% of hESC colonies containing cells positive for TH, a critical catecholaminergic enzyme, after three weeks of differentiation.

Two potential drawbacks may limit the therapeutic application of ESCs. First, the generation of hESCs requires fertilized eggs from donors and the destruction of early embryos, which raises a plethora of ethical and legal concerns. Second, hESC-derived grafts are allogeneic to recipient patients, thus making immuno-suppressive regimens necessary (Leng & Tian, 2016). Despite these limitations, hESCs are currently the "gold standard" of SCT for PD, and hESC-derived midbrain DA (mDA) neurons are currently being developed for clinical trials in the USA and Europe (Kern et al., 2018; Weick et al., 2011). Chinese scientists have also initiated clinical trials of ESC-based therapy for PD (Cyranoski, 2017).

Induced pluripotent stem cells (iPSCs)

iPSCs are adult somatic cells that are converted into pluripotent cells via the introduction of specific transcription factors found in normal PSCs. The cells can be differentiated into most somatic cell types and are self-renewable (Zhang et al., 2019). As recently as five years ago, direct therapeutic treatment of PD through transplantation of iPSCs was not feasible. Transplantation faced many problems such as low efficiency, virus requirements, and teratoma development (Li et al., 2015b). Attempts to use xenogeneic materials resulted in contamination by animal-source pathogens, which can cause an immune response after transplantation in humans (Bergstrom et al., 2011). However, researchers have since developed a xeno-free medium alongside a feeder-free culture system and cre-mediated excision of reprogramming factors to obtain transgene-free iPSCs with improved efficiency (0.15%−0.3%) (Lu et al., 2014). Although more testing is needed, especially in animal models, these results suggest that iPSCs are more viable than previously thought from an efficacy standpoint (Li et al., 2015b).

Recent progress in clinical treatment shows promise in animal models of PD. For example, Han et al. (2015) found that human iPSCs transplanted into 6-OHDA-induced parkinsonian rats improved functional "rotational asymmetry" defects several weeks after transplantation. In another study, iPSC-derived DA neurons were transplanted into parkinsonian cynomolgus monkeys and survived for two years over the length of the study; in addition, the transplanted DA neurons reinnervated the host brains, grew into the putamen, and showed long-term viability (Hallett et al., 2015). Although the results were only positive for one of the three tested monkeys, the study demonstrated that iPSC-derived DA neurons can be used for transplantation with long-term improvement in motor function without immunosuppression (Hallett et al., 2015).

Kikuchi et al. (2017) transplanted neurons derived from iPSCs into NHP brains and found that symptoms improved significantly after two years of tracking the monkeys. Morizane et al. (2017) also transplanted grafted DA neurons induced by cynomolgus iPSCs into allogeneic NHP PD models. Different from Kikuchi et al. (2017), who used FK506 (immune inhibitor) to reduce immune rejection, Morizane et al. (2017) used major histocompatibility complex (MHC)-matched allogeneic neural cell grafting in the brain, which is considered a less immune-responsive tissue, using iPSCs derived from MHC homozygous cynomolgus macaques. Furthermore, immunohistological analyses revealed that MHC-matching reduced the immune response by suppressing the accumulation of microglia (Iba-1+) and lymphocytes (CD45+) in the grafts (Morizane et al., 2017). These studies have made great contributions to cell transplantation.

Mesenchymal stem cells

Therapeutic stem cell studies have often utilized multipotent mesenchymal stem cells (MSCs) rather than ESCs, the use of which poses ethical concerns. Bone marrow, umbilical cord blood, and adult adipose-derived stromal tissue have been used as sources of MSCs for autologous grafts (Fallahi et al.,

2007; Park et al., 2015).

Using human umbilical MSCs, Wang et al. (2011) showed the potential of this approach for PD treatment. Specifically, human MSCs isolated from Wharton's jelly of the umbilical cord were induced to transform into DA neurons *in vitro* through stepwise culturing in neuron-conditioned medium, resulting in a 12.7% success rate, as characterized by positive staining for TH and dopamine released into the culture medium. When these cells were transplanted into the striatum of parkinsonian rats (induced by unilateral striatal lesioning with 6-OHDA), the transplantation partially corrected lesion-induced amphetamine-induced rotation, with the cells showing viability for at least four months. Furthermore, Wang (2011) also found MSCs showed protective effects on progressive DA neural loss *in vitro* and *in vivo*. Treatment decreased MG-132-induced DA neuronal loss with a significant reduction in caspase-3 activity. Subsequently, application of hMSCs in MG-132-treated rats dramatically reduced the decline in the number of TH-immunoreactive cells, with an almost 50% increase in the survival of these cells in the substantia nigra (Wang et al., 2011). Furthermore, hMSC treatment significantly decreased OX-6 immunoreactivity and caspase-3 activity (Park et al., 2015). While MSC transplantation may be effective in modulating the immune response in neurodegenerative diseases, it is highly unlikely that MSC-derived neurons will ever be used for cell replacement therapy (Xu et al., 2012). Treatment with MSCs suppresses autoimmunity and restores salivary gland secretory function in both mouse models and Sjogren syndrome patients (Xu et al., 2012). MSC treatment directs T cells toward Treg and Th2, while suppressing Th17 and Tfh responses, and can alleviate disease symptoms (Xu et al., 2012). Collectively, the immunological regulatory functions of MSCs play an important role in Sjogren syndrome pathogenesis, and allogeneic MSC treatment may provide a novel, effective, and safe therapy for patients with this syndrome.

Neural stem cells

Neural stem cells (NSCs) are multipotent cells capable of differentiating into both neurons and glial cells. By using a monkey model, a group reported that the engrafted newborn neurons could functionally integrate into the host neuronal network, and this had proved that transplantation of NSCs may be a valid way for curing brain injuries (Wang et al., 2017; Wei et al., 2017). There are two ways to obtain human NSCs (hNSCs), i. e., directly from the brain (Abe et al., 2016) and differentiated from other cells, including stem (Kim et al., 2004) and somatic cells (Ai et al., 2016). Bjugstad et al. (2005) transplanted hNSCs into the caudate and substantia nigra of MPTP-induced PD monkeys and concluded that hNSCs may be beneficial for maintaining a normal environment. Their research group also analyzed the differentiation and migration ratio of hNSCs transplanted into the body (Bjugstad et al., 2008; Kern et al., 2011). These studies provide an important basis for the clinical application of hNSCs.

Recent studies have indicated that certain NSCs persist in the adult nervous system and are capable of regenerating new neurons (Bacigaluppi et al., 2016; L'episcopo et al., 2018). Compared with pluripotent stem cells, multipotent NSCs exhibit higher cellular survival rates and lower risk of teratoma formation (Pardal & Barneo, 2012). In addition to the fetal isolation of NSCs, these cells can be obtained from areas of the adult brain, including the subventricular zone, subgranular zone, and hippocampus (Wang et al., 2012). Acquisition of NSCs from non-fetal sources avoids the ethical issues associated with the use of ESCs. Because NSCs can self-renew and differentiate into many types of neurons, including those that are dysfunctional in neurodegenerative diseases, their potential use in the treatment of patients with PD is promising (Choi et al., 2017).

FUTURE DIRECTIONS OF NHP-ENABLED SCT RESEARCH

NHPs are similar to humans in size, behavior, physiology, biochemistry, and immune functions (Vierboom et al., 2012; Zhang et al., 2014). Due to their many advantages, NHP models of PD can compensate for the deficiencies in SCT clinical trials of PD and provide vital information unavailable from rodent models, such as cellular migration, survival, and differentiation after transplantation, choice of target sites, and timelines of recovery (Vermilyea & Emborg, 2018). To date, however, all NHP-based studies on CBT for PD have been performed in neurotoxin-induced PD models. Validating state-of-the-art, recently available genetic models are anticipated to facilitate the development of SCT for PD and its clinical translation.

Different types of stem cells, including ESCs, NSCs, MSCs, and iPSCs, can be used for specific cellular therapeutic approaches. Multiple factors can differentiate these cells into DA neurons, which can be used to replace damaged neurons in PD patients. Methods for inducing differentiation depend upon the type of stem cell. Furthermore, risks such as tumor formation remain after transferring DA cells into PD patients. ESCs and iPSCs have advantages over the other two stem cell types. For example, ESCs remain highly proliferative *in vivo* and can survive and generate DA neurons after transplantation. In turn, iPSCs can generate unlimited, PD patient-specific cells, and produce a degree of functional host recovery after transplantation (Morizane et al., 2017).

Graft distribution could also benefit from NHP-based studies and noninvasive imaging approaches. For example, Silvestrini et al. (2015) used real-time intraoperative magnetic resonance imaging (MRI) to monitor cell transplantation into a swine and cadaveric human head for possible application in the human brain. Furthermore, Malloy et al. (2017) used an MRI-compatible delivery system to monitor the distribution of cells pre-labeled with a contrast agent into the basal ganglia of a baboon. These new MRI-based imaging methods can increase the safety and accuracy of grafting procedures and facilitate the evaluation of different target sites.

In addition to the challenges mentioned above, many

questions remain to be answered in order to improve effective SCT for PD. For example, the influence of cell preparation and storage on engraftment, method of transplantation, choice of target sites, and timelines of recovery are basic parameters that still require evaluation in NHP models to improve SCT for PD and its translation into clinical treatment.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.Y.N. and Z.Z.C. wrote and revised the manuscript. All authors read and approved the final version of the manuscript.

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